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BONE MARROW FAILURE SYNDROMES

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The diagnosis of a patient who has a bone marrow failure syndrome is often difficult and relies on the clinical observation of a phenotype that then leads the physician to request laboratory tests that are of variable specificity. A very small number of the genes or gene loci have been identified, and unique diagnostic tests are available for only a few disorders. The marrow failure syndromes are often inherited with known genetic patterns, but they may be sporadic in some cases. Despite being inherited, they are not always congenital, i.e., present at birth, and thus the term inherited is preferred. It is important to include some clinical features in this discussion, because they lead to the appropriate laboratory tests. Tables 1 through 5 below summarize the clinical, hematologic, and genetic findings for the most common syndromes and mention specific tests where appropriate. Details regarding phenotypes, pathophysiology, and treatment can be found in recent reviews,[8, 67] and most citations in this article are to critical recent papers. Remember that many of these syndromes might be diagnosed from their physical appearance long before they develop hematologic problems and that the latter are quite nonspecific. Unfortunately, however, it is often only after cytopenias or malignancies have developed that the combination of physical findings and hematologic disease triggers the consideration of a specific bone marrow failure syndrome.

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PANCYTOPENIA

Patients who have many of the syndromes present initially with involvement of a single lineage and later progress to pancytopenia. The conditions to be discussed in this section include all those in which at least some, if not all, patients do develop aplastic anemia. The disorders in which there is only a single cytopenia are discussed in a later section.

Fanconi's Anemia

The disorder Fanconi's anemia (FA) was initially identified as an association between aplastic anemia in children and a specific constellation of birth defects (Table 1) that particularly involve skin pigmentation, short stature, and radial anomalies. This clinical phenotype sufficed for diagnoses from the first description in 1927 through the next 40 or more years. In the mid-1960s, several groups observed chromosome breakage in examination of the karyotypes of dividing lymphocytes, now referred to as spontaneous breaks. Although the underlying biochemical defect in FA is still not clear, there is an apparent defect in DNA repair. By the early 1980s it was recognized that the frequency of chromosome breaks, gaps, rearrangements, exchanges, endoreduplication, and quadriradials was significantly increased if the cells were cultured in the presence of DNA crosslinkers, called clastogenic agents. After the introduction of this type of laboratory test, cases were diagnosed that lacked some or all of the physical findings, and data from the International Fanconi Anemia Registry suggest that as much as one third of patients who had FA may not have birth defects.[27] Even this is an underestimate because, to have been tested initially, patients most likely had either aplastic anemia or an affected sibling.

Useful radiologic studies include skeletal X rays, which may identify both obvious and occult abnormalities, as well renal ultrasound to identify structural kidney defects. Brain studies performed with computerized tomography (CT) or magnetic resonance imaging (MRI) may also reveal congenital problems.

The hematologic findings in FA are quite nonspecific (Table 2); symptoms usually begin at an average of 8 to 9 years of age but range from birth to the sixth decade.[38] Patients often present with thrombocytopenia or anemia, which then progresses to pancytopenia. The anemia is macrocytic, and fetal hemoglobin (HbF) is elevated, as seen in other conditions with stress erythropoiesis.[3] Bone marrow appearances vary, related to the degree and the type of cytopenia, but generally are hypocellular, with reduced or absent megakaryocytes. Marrow biopsies are best used to assess cellularity and aspirates to evaluate cellular morphology. In perhaps 10% to 25% of cases there is evidence for myelodysplastic syndrome (MDS) with dysplasia, myeloperoxidase deficiency, dual-esterase positivity, periodic acid Schiff (PAS)-positive erythroblasts, or even ring sideroblasts. Clonal cytogenetic abnormalities may also be found. Hematopoietic cultures are nonspecific, and show reduced colony formation (Table 3) that may partly correlate with the clinical severity and that

Table 1. PHYSICAL ANOMALIES IN PATIENTS WHO HAVE BONE MARROW FAILURE SYNDROMES

Disorder (N)	Anomalies (% of Patients)	Imaging Studies
Pancytopenia		
FA* (1000)	Hyperpigmentation and/or café au lait 60%, shortness 57%, radius and/or thumb 48%, male hypogonadism 37%, microcephaly or other head anomalies 27%, eyes 26%, renal 23%, developmental delay 13%, low birth weight 12%, ears 10%, lower limbs 9%, other skeletal 7%, cardiopulmonary 7%	Skeletal survey, renal ultrasound, CNS, MRI or CT
DC* (225)	Reticular hyperpigmentation 95%, dystrophic nails 93%, mucous membrane leukoplakia 73%, epiphora 44%, teeth carious and/or early loss 23%, developmental delay 16%, osteoporosis and aseptic necroses 14%, hyperhidrosis 14%, shortness 12%, urethral anomalies 11%, esophageal and other gastointestinal 10%, male gonads 5%	Head X rays for CNS calcifications, skeletal survey for osteoporosis and aseptic necroses
SD* (200)	Shortness and malnourished >60%, metaphyseal dysostosis 30%, developmental delay 15%, myocardial fibrosis 6%	Skeletal survey for metaphyseal dysplasia, pancreatic ultrasound, CT or MRI for lipomatosis
CHH* (250)	Short-limbed short stature caused by metaphyseal chondrodysplasia 100%, hypoplastic hair >90%	Skeletal survey for metaphyseal dysplasia
PS* (50)	Shortness and malnourished ~50%	
RD* (20)	No lymph nodes or tonsils 100%	Imaging for absent lymphoid tissue
Amega* (50)	Developmental delay 30%, congenital heart disease 14%, microcephaly 11%, cerebral or cerebellar atrophy 11%	Skeletal survey, CNS imaging
Familial (~150)	Depends on the syndrome, includes radial hypoplasia in IVIC, ulnar anomalies in WT, radioulnar dysostosis, cerebellar atrophy, etc.	Skeletal
Single Cytopenia		
DBA (550)	Microcephaly, cleft palate, short neck, 12%, low birth weight 8%, thumbs 9%, shortness 6%, eyes 6%	Skeletal
KS (200)	Shortness, developmental delay, cataracts, microcephaly all <10%	
TAR (200)	Radii absent 100%, ulnae 49%, humerae 34%, hands 49%, legs 41%, gastrointestinal 18%, head 14%, feet 12%, spine 12%, cardiac 11%, hemangioma 10%, eyes 6%, ears 6%, gonads 5%, web neck 5%	Skeletal

*See text for definitions of abbreviations of disease names. Anomalies are mentioned if they were found in ≥5% of patients. If no description is given, various abnormalities were reported. Details can be found in other reviews.[8, 67]

Table 2. HEMATOLOGIC FINDINGS IN PATIENTS WHO HAVE BONE MARROW FAILURE SYNDROMES

Disorder	Median Age Hem (Yrs)	% with Aplastic Anemia	First Lineage Affected	Marrow	HbF	MCV
Pancytopenia						
FA*	7.5	>90%	Any	Aplastic	↑	↑
DC*	16	50%	Any	Aplastic	↑	↑
SD*	<4	25%	Neutropenia; chronic, intermittent, or cyclic	Hypocellular, myeloid arrest	↑	↑
CHH*	Child		Anemia 87%, lymphopenia 60%, neutropenia 25%	Erythroid hypoplasia, maturation arrests	↑	↑
PS*	<1	50%	Anemia 70%, neutropenia 50%, thrombocytopenia 50%	Vacuoles in precursors, ring sideroblasts	↑	↑
RD*	Birth	~50%	Neutropenia and lymphopenia 100%, anemia 50%	Aplastic		
Amega*	1 wk	40%	Thrombocytopenia	Absent or small megakaryocytes	↑	↑
Familial		Various	Any	Various	↑	↑
Single Cytopenia						
DBA*	2 mo		Anemia	Erythroid hypoplasia	↑	↑
KS*	1 mo		Neutropenia, increased eosinophils, and monocytes	Promyelocyte-myelocyte arrest		
TAR*	Birth		Thrombocytopenia	Absent or small megakaryocytes		

*See text for definitions of disease names.
Details can be found in other reviews.[8, 67]

Table 3. HEMATOPOIETIC CULTURES IN PATIENTS WHO HAVE BONE MARROW FAILURE SYNDROMES

Disorder	CFU-E	BFU-E	CFU-GM	CFU-Mk	Effective Cytokines
Pancytopenia					
FA*	↓↓	↓↓	↓↓		SCF* ↑
DC*	↓↓	↓↓	↓↓		SCF* ↑
SD*	↓↓	↓↓	↓↓		G-CSF* ↑
CHH*	↓	↓↓	↓	↓↓	
PS*	↓↓	↓↓	↓		Ep,* G-CSF, SCF ↑
RD*	↓↓	↓↓	↓↓		
Amega	↓	↓	↓	↓↓	IL-3* + GM-CSF* ↑, TPO* not ↑
Familial	↓	↓	↓		
Single Cytopenia					
DBA*	↓↓	↓↓	Normal		Ep, IL-3, SCF, IL-9 ↑
KS*	Normal	Normal	Normal or ↓ (eosinophils, monocytes, immature myeloids, absent or rare neutrophils)		G-CSF ↑ differentiation
TAR*	Normal	Normal	Normal	↓↓	TPO not ↑

Legend: CFU-E: Colony-forming units—erythroid; BFU-E: Burst-forming units—erythroid; CFU-GM: Colony-forming units—Granulocyte macrophage; CFU-Mk: Colony-forming units—Megakaryocyte.

*See text for definition of abbreviations.

Details can be found in other reviews.[8, 67]

may improve with the addition of some cytokines, such as stem-cell factor (SCF).[6, 7] Serum erythropoietin (Ep) levels are increased much more than expected for the degree of anemia,[67] as are tumor necrosis factor-α[56] and flt3 ligand.[43] SCF and granulocyte-macrophage colony-stimulating factor (GM-CSF) were decreased.[66] At least 10% of FA patients have leukemia (usually myeloid), either at presentation or subsequently, and the prediction is that a substantially higher number may undergo this evolution.[15] In addition, at least 10% of FA patients develop solid tumors or liver cancer, and thus FA is truly a premalignant condition (Table 4).[5]

The inheritance of FA is autosomal recessive, with at least eight different genes involved, according to results of complementation analysis.[34] In these studies, hybrid cells from patients of different complementation groups, and hence different mutations, mutually correct the chromosome fragility, whereas cells from patients from the same group retain their fragility. Because they require immortalization of cell lines (with Epstein–Barr virus) and the introduction of genes for selection markers to permit recovery of hybrid cells, these assays are not trivial. Complementation studies are only used in research laboratories, not for routine diagnoses.

Diagnostic testing (Table 5) relies mainly on the use of clastogenic agents, usually diepoxybutane[10] (DEB) or mitomycin C (MMC).[17] Peripheral blood lymphocytes are cultured in the presence of a T-cell mitogen, such as phytohemagglutinin, for 72 to 96 hours, with exposure to DEB or MMC for the last 24 to 48 hours. Standard metaphase preparations are made, and the cells are scored for aberrations; data are reported as mean breaks per cell, the proportion of cells with breaks, radial figures per cell, or the proportion of cells with radials. Typical examples are shown in Figure 1. Bone marrow is less often positive than is peripheral blood, perhaps because the usual approach to marrow karyotypes is either uncultured cells or cells cultured for only 24 hours; thus it relies on the demonstration of breaks in cells undergoing metaphase in vivo rather than accumulating in vitro. Another useful cell type is skin fibroblasts; they require more effort both to obtain and to analyze than do lymphocytes but are important for diagnosis in cases with hematopoietic mosaicism (see below).

Several laboratories have reported that the progression of FA cells through cell cycle is delayed, with an accumulation at G2/M after culture with a clastogen such as nitrogen mustard.[9, 12] One adaptation of this utilizes a nitrogen mustard dose response curve in which a higher proportion of FA cells accumulates at G2/M at a lower concentration of clastogen than is maximal in normal cells.[12] All known FA patients were abnormal, and non-FA controls such as acquired aplastic anemia and dyskeratosis congenita were normal. With the expansion of fluorescence-activated cell sorting (FACS) into the clinical laboratory arena, this approach requires consideration, because it is less labor intensive than light microscopic breakage analysis.

Two of the FA genes have been cloned, and a third has been

Table 4. MALIGNANCIES IN PATIENTS WHO HAVE BONE MARROW FAILURE SYNDROMES

Disorder	Leukemia	MDS	Solid Tumor	Liver Tumor
Pancytopenia				
FA*	10%: acute myeloid 87%, acute lymphocytic 4%, unspecified 11%	6%: refractory anemia 50%, refractory anemia with excess blasts 50%, clonal cytogenetics >90%	5%: oropharyngeal 27%, gastrointestinal 29%, gynecologic 20%, brain 7%, other 16%	3%: hepatocellular carcinoma 69%, adenoma 24%, unspecified 7%
DC*	1%: acute myeloid		10%: oropharyngeal 39%, gastrointestinal 30%, other 30%	
SD*	5%: acute myeloid 71%, acute lymphocytic 21%, other 8%	4%, especially monosomy 7		
CHH*			6%: Hodgkin's disease, basal cell carcinomas, lymphoma, lymphosarcoma, testicular tumor	
PS*				
RD*				
Amega*	5%			
Familial	varied, usually myeloid	varied	varied	
Single Cytopenia				
DBA*	2%: acute myeloid 90%, acute lymphocytic 10%	0.2%	2%: Hodgkin's disease, breast, hepatoma, stomach, osteogenic sarcoma, vaginal melanoma	
KS*	10%	5%		
TAR*	0.5% (ALL)			

*See text for definitions of disease abbreviations.

The first percentage in each column is the percentage of that disease reported with that category of malignancy. Where available, the subsequent percentage data are the percentage of those within that category. Data are approximate, since the denominators may be incomplete. Details can be found in other reviews.[8, 15, 67]

Table 5. GENETICS AND DIAGNOSTIC TESTS IN PATIENTS WHO HAVE BONE MARROW FAILURE SYNDROMES

Disorder	Genetics	Gene(s) or Loci	Diagnostic Tests	Prenatal Diagnosis
Pancytopenia				
FA*	AR	A = 16q24.3, C = 9q22.3, D = 3p22–26, B, E-H not mapped	Chromosome breaks with MMC* or DEB,* or mutational analysis or flow cytometry	Same, ultrasound re: radii, thumbs, and kidneys
DC*	XLR 75%, AR 13%, AD 12%	Xq28	Haplotype, fibroblast culture	Haplotype
SD*	AR		Marrow, X rays, pancreatic imaging, serum trypsinogen	?Neutropenia, metaphyseal dysostosis by ultrasound
CHH*	AR	9p21-p13	X rays	Metaphyseal dysostosis by ultrasound, haplotype
PS*	Mitochondrial	Respiratory enzyme mt DNA	Marrow vacuoles, mt DNA	mt DNA
RD*	AR		Marrow	
Amega*	XLR, AR	c-mpl	Marrow	Thrombocytopenia
Familial	XLR, AR, AD, sporadic		Marrow	
Single Cytopenia				
DBA*	Sporadic, AR, AD	19q13	Marrow, ADA*	?ADA, ?anemia
KS*	AR		Marrow	?Neutropenia
TAR*	AR, rare AD		Marrow	U/S, thrombocytopenia

*See text for definitions of abbreviations.
Details can be found in other reviews.[8, 67]

mapped. The gene for the Fanconi Anemia Group C (FAC) was cloned and mapped to 9q22.3 in 1992,[58, 59] and the Fanconi Anemia Group A (FAA) gene was cloned and mapped to 16q24.3 in 1996,[41, 62] while the FAD gene has been mapped to 3p22-26, but it has not yet been cloned.[65] To date, the cloned genes have not provided a molecular pathophysiologic explanation for the FA phenotype. Neither the FAA nor the FAC proteins are found in the Human Genome Database. Recent studies suggest that FAA and FAC, which are primarily cytoplasmic, do form a nuclear complex[37] but their precise role in DNA repair has not yet been clarified.

A combination of molecular and complementation analyses has been used to suggest that the majority of patients are FAA mutants, with FAC being the next most frequent. In North America, group A patients are 69%, group C 18%, group D 4%, and group B or E to H 9%.[33] Molecular tools include Southern blotting, oligonucleotide hybridization, restriction-site assays, amplification refractory mutation, chemical cleavage mismatch analysis, and single strand conformational polymorphism. Positive results (with exclusions of silent polymorphisms) are diagnostic of FA in a candidate patient, but negative results do not exclude FA because the mutation may not have been identified. Molecular methods can be used for carrier detection, both within a candidate family and for population screening, such as the IVS4 A→T mutation found in 1% of Ashkenazi Jews in New York.[63] Genotyping of patients will lead to genotype–phenotype correlations.[28]

Prenatal diagnosis of FA can be done by analysis of clastogen-induced chromosome breakage in cultured amniotic or chorionic villus fibroblasts or in fetal lymphocytes obtained by percutaneous umbilical blood sampling.[10] More precise and faster information can come from DNA-based diagnoses in situations in which the mutation has been identified in a propositus or in the carrier parents.

Somatic mosaicism was recently identified as a cause of false-negative diagnoses.[40] As many as 25% of patients may have a mixture of lymphocytes that are highly sensitive to DNA crosslinkers and cells that show a normal level of sensitivity. In the extreme, the residual sensitive population is too rare to permit accurate diagnosis of FA. This mosaicism is at the level of hematopoietic cells, because fibroblasts from such patients retain their diagnostic sensitivity. Among 8 patients with mosaicism, 3 were compound heterozygotes for FAC mutations. These 3 patients had intragenic recombination caused by an intragenic crossover or by gene conversion. Most of the patients had mild hematologic disease, consistent with in vivo corrected hematopoiesis.

The most difficult problem in the diagnosis of FA is determining which patients to test. In an ideal world, anyone, including adults, with aplastic anemia or nonimmune thrombocytopenia or red-cell aplasia is a candidate. It could be argued that anyone who has a characteristic birth defect (Table 1), such as thumb or radial anomalies, should also be tested because diagnosis prior to development of cytopenias, myelodysplastic syndrome, or leukemia may permit early and correct treatment when hematologic events do develop.[4] Early diagnosis also provides

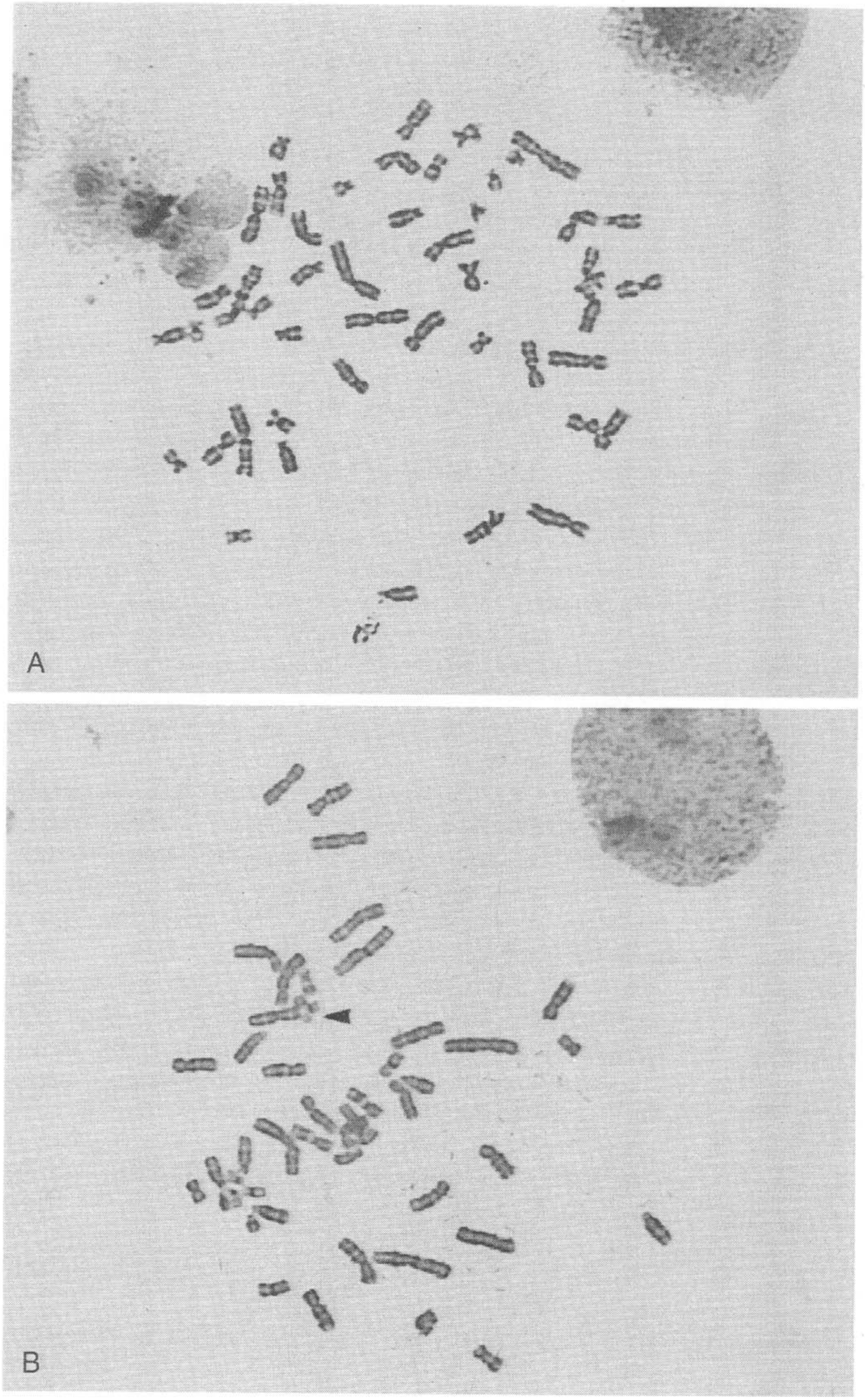

Figure 1. Chromosome breaks in FA, using lymphocytes cultured with, *A*, no clastogen, *B*, 100 ng/mL DEB, and *C*, 20 ng/ml MMC. Arrowheads point to chromosomal aberrations. (Courtesy of Jerome McCombs, PhD, University of Texas Medical Branch, Galveston, Texas.)

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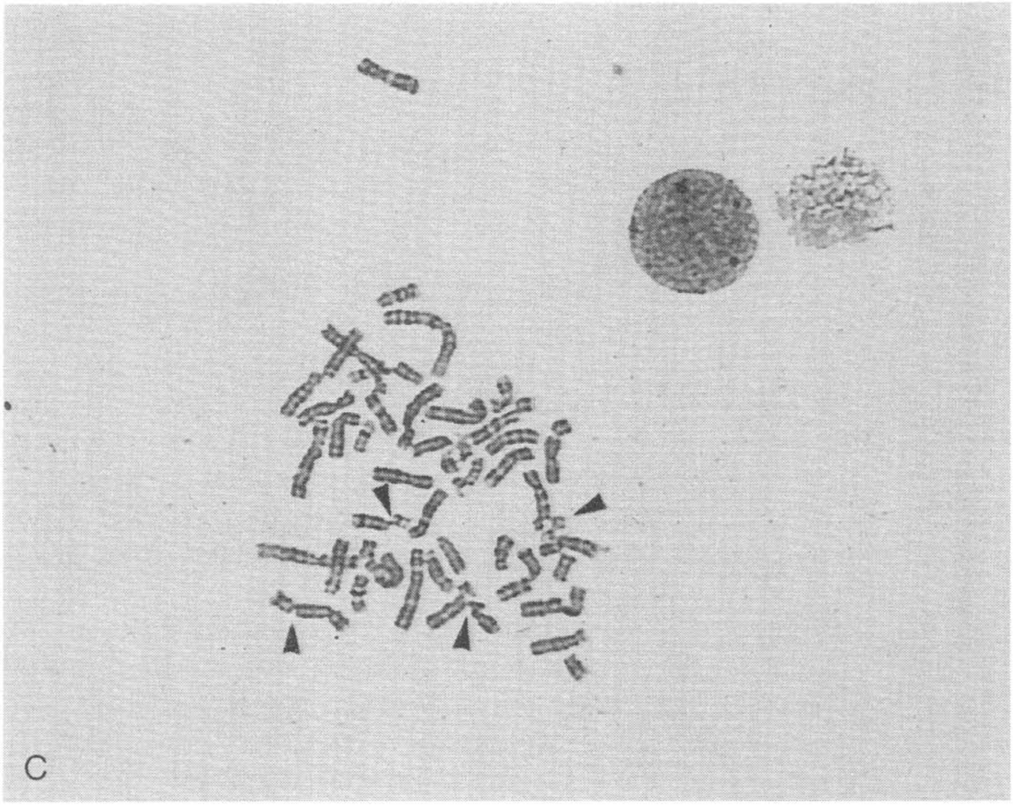

Figure 1 *(Continued).*

genetic information to families who wish to have more children or whose next pregnancy might provide cord blood for a stem-cell transplant. The physician needs to know if a transplant recipient is FA, because the immunosuppression must be reduced, and it must be known if a transplant donor is FA negative because an affected donor does not successfully engraft.[54] It might be useful to test for FA in anyone who develops acute myeloid leukemia, myelodysplasia, or a solid tumor at an age younger than the general population (Table 3), because FA patients are at higher risk.[5]

Dyskeratosis Congenita

Patients who have dyskeratosis congenita (DC), in contrast to those who have FA, have a different constellation of physical findings, such as dystrophic nails, reticular pigmentation, and leukoplakia (Table 1). However, some of the older literature reports of FA probably included patients who had DC.[23, 24] One of the diagnostic problems in DC is that the characteristic phenotype evolves with age, and hematologic findings may precede physical ones. Approximately half of DC patients do develop aplastic anemia at a median age of 16 years (Table 2), and the aplasia cannot be distinguished morphologically from any other aplastic anemia. Peripheral blood and marrow findings are nonspecific, and hematopoietic colony formation is reduced (Table 3). Myelodysplasia and leukemia can also occur in DC patients, and in ~15% of reported cases, solid tumors developed at ages younger than in the general population (Table 4). Skin biopsies show epidermal atrophy with melanophages in the upper dermis, but this is not pathognomonic.[42] Radiography may be useful to find central nervous system (CNS) calcifications, osteoporosis, or aseptic necroses.

Most cases of DC are X-linked recessive, but there are apparent autosomal recessive and dominant cases as well (Table 5). The gene has been mapped to Xq28,[36] and skewed X inactivation was found in female carriers.[18] Some males who have DC can therefore have the clinical diagnosis supported by appropriate linkage studies, and finding random X inactivation in obligate carriers might suggest that it was a new mutation or that the disease is not X linked in that family. Prenatal testing should be possible in families in which Xq28 haplotype analysis is useful.

The clastogenic stress test for chromosome instability that is diagnostic in FA is negative in DC. Although various small studies suggested that DC lymphocytes might be sensitive to other agents, such as bleomycin, the consensus is that they are probably normal.[20] However, those authors do suggest that there is chromosomal instability in DC and report that DC fibroblasts have abnormal morphology (polygonal cells, ballooning, and dendriticlike projections) and a slower growth rate than normal cells.

Shwachman-Diamond Syndrome

Patients who have Shwachman-Diamond syndrome (SD) are usually seen by a gastroenterologist for their failure to thrive and for malabsorption (Table 1) long before they are noted to have neutropenia or other hematologic signs.[44, 57] The major physical manifestation is steatorrhea from exocrine pancreatic insufficiency (caused by acinar cell hypoplasia), poor growth that may be inherent and not caused by malnutrition, and delayed development. Neutropenia, defined as less than 1500 neutrophils/μL on at least one occasion, may be chronic, intermittent, or cyclic. Although many SD patients may not need a hematologist, a large minority will develop aplastic anemia, leukemia (usually myeloid), or MDS (Tables 2 and 4). The incidence of these events increases with age and may become more apparent as the cohort of patients known to have SD gets older.

SD patients may have any combination of neutropenia with anemia, thrombocytopenia, or depression of all three lineages. Bone marrow examination during neutropenia may show decreased cellularity or a myeloid maturation arrest. As in other marrow failures, HbF and mean corpuscular volume (MCV) are often elevated. Hematopoietic cultures may show decreased colony formation, and myeloid colonies often increase with the addition of granulocyte colony-stimulating factor (G-CSF).

Tests for pancreatic insufficiency include low or absent duodenal trypsin, amylase, and lipase, and serum cationic trypsinogen may also be decreased; fecal fat losses are more than 15% in those below 6 months of age and 7% in older children.[44] Liver function tests may be abnormal, because of an element of cholestasis, which improves with age. Pancreatic insufficiency also improves with age, and the older patient may have normal test results. The Toronto group reported that quantitative pancreatic stimulation with intravenous secretin and cholecystokinin, followed by measurement of duodenal colipase, lipase, and trypsin, remained below normal regardless of clinical pancreatic function.[44]

Radiologic studies identify sites of metaphyseal dysplasia, which may be of clinical importance. Pancreatic lipomatosis should be present in all cases and may be seen with ultrasound (hyperechogenic), CT, or MRI. The MRI is considered the most specific, with hyperintense T1- and T2-weighted images, and features characteristic of fat.[39]

SD inheritance is autosomal recessive, but to the best of the author's knowledge, there is no published information with regard to gene localization or identification. Individuals who might be tested include all children with unexplained neutropenias or other cytopenias, with or without metaphyseal dysplasia and with or without overt pancreatic insufficiency. Unfortunately, the tests are not totally specific, but cumulative results may lead to SD as the most likely diagnosis. Prenatal testing might be offered to families with a propositus and include fetal blood counts and ultrasound for metaphyseal dysplasia. However, since the neutrophil count is normally very low in early pregnancy,[26] it may not be possible to make a definitive diagnosis of fetal neutropenia.

Cartilage-Hair Hypoplasia

First described among the Amish, cartilage-hair hypoplasia (CHH) was later noted to have a high prevalence in the Finnish as well.[45, 46] It is an autosomal recessive condition with metaphyseal chondrodysplasia leading to short-limbed dwarfism, hypoplastic hair, defective immunity, and anemia. The patients have short stature, laxity of joint ligaments, and often scoliosis or lordosis (Table 1). Hair is fine and sparse. Radiography demonstrates metaphyseal flaring and irregularities, as well as other skeletal changes. Microscopic examination of hair shows an absence of a central pigment core.

Hematologic findings (Table 2) include lymphocytopenia in 60% of affected patients and impaired response to phytohemagglutinin, indicating a deficiency in T-cell function; there is poor response to B-cell mitogens and defective soluble immunity as well.[52] One fourth of CHH patients have neutropenia. Approximately 80% have macrocytic anemia, with 16% of the Finnish patients having severe anemia and requiring transfusions. Bone marrow aspirates and biopsies range from erythroid hypoplasia to erythroid or myeloid maturation arrests to normal. Hematopoietic colony formation is reduced, even in patients who have normal blood counts and normal marrow morphology (Table 3). Although leukemia and myelodysplasia have not been observed in CHH, several solid tumors were reported (Table 4).

The gene for this autosomal recessive condition was mapped to 9p21-p13,[60] and prenatal diagnosis was performed successfully in 4 cases by haplotype analysis. These diagnoses were confirmed by ultrasonography.[61]

CHH should be suspected in a patient who has metaphyseal chondrodysplasia and hematologic findings, who does not have the malabsorption described above in SD, and who, in particular, has hypoplastic hair. Radiographic findings are characteristic although not totally specific. DNA haplotyping may be confirmatory.

Pearson's Syndrome

Patients who have Pearson's syndrome (PS) do not have pathognomonic physical findings, although they are often short and malnourished (Table 1).[50] The pancreatic involvement may include both exocrine insufficiency as well as metabolic acidosis and insulin-dependent diabetes. Anemia is the most frequent hematologic problem, although neutropenia was the sign first noted, and thrombocytopenia is also common (Table 2). The hallmark of the hematopathologic diagnosis of PS relies on the finding of cytoplasmic vacuoles in myeloid and erythroid precursors in the marrow, combined with ring sideroblasts. It might be wise to look for PS in any children who have MDS with ring sideroblasts. Hematopoietic cultures show reduced numbers of colonies, with improvement in the presence of some cytokines (Table 3). Nonspecific laboratory tests depend on which organs are clinically involved and include tests for diabetes, lactic acidosis, renal Fanconi's syndrome, and liver failure. No malignancies have been reported in PS to date.

The specific diagnosis of PS is made at the molecular level with the demonstration of a deletion of mitochondrial DNA that involves the genes for respiratory enzymes.[55] The deletion ranges from 2.7 to 7.767 kb and is 4.977 kb in the majority of the patients. Southern blotting with the appropriate probes suffices for the diagnosis. Mitochondrial inheritance is maternal, although very few affected mothers and no siblings have been reported. Prenatal testing could be offered, however, with DNA from fetal blood, chorionic villi, or amniocytes being used. A history of fetal hydrops has been observed in a few cases. The variety of clinical phenotypes and of different organ systems involved is related to the fact that every cell has many mitochondria, and there is heterotopic segregation of normal and abnormal mitochondria at each cell division; the most affected organs have a large proportion of cells, which, in turn, have a large proportion of abnormal mitochondria.

PS candidates are children who suffer from malnutrition, acidosis, and cytopenias with vacuolated precursors. It also includes those who have MDS with ring sideroblasts.

Reticular Dysgenesis

Initially called thymic alymphoplasia with aleukocytosis, reticular dysgenesis (RD) is diagnosed in newborns who have congenital agranulocytosis, lymphopenia, and absent cellular and humoral immunity. The sex ratio is 4:1 male:female, suggesting that X-linked recessive inheritance may predominate. Imaging studies show that the patients lack lymph nodes and thymus (Table 1). All patients have neutropenia and lymphopenia, and anemia is common, whereas thrombocytopenia is less so (Table 2). The bone marrow is hypocellular, with no myeloid or lymphoid precursors, whereas erythroid aplasia is often seen. Progenitor cell assays show absent or very reduced colony formation (Table 3), supporting the implication that RD is caused by a defect at the level of the pluripotent hematopoietic stem cell. Although no prenatal diagnoses have been reported, demonstration of absent lymphocytes and neutrophils in a fetal blood sample might be highly suggestive.

Amegakaryocytic Thrombocytopenia

Although the majority of patients who have amegakaryocytic thrombocytopenia (amega) have normal physical examinations, a subset have microcephaly and cerebellar or cerebral atrophy, as well as developmental delay or congenital heart disease (Table 1). Thrombocytopenia is usually noted within the first week, and macrocytosis with increased HbF is common, suggesting a broader level of marrow involvement than the platelet lineage alone (Table 2). Initially, bone marrow examination shows normal cellularity, with absent or decreased megakaryocytes, which when present are small and inactive. Platelet survival is normal. Evolution to pancytopenia occurs in approximately 50% and is associated with development of marrow hypocellularity and aplasia. The serum level of thrombopoietin (TPO) is much higher in amega than in normal control subjects.[49] Cultures of megakaryocyte colonies show reduced numbers, with some improvement with Interleukin-3 (IL-3) plus GM-CSF, but not with TPO[31, 49] (Table 3). Leukemia is a potential evolution for the amega patient who does not succumb during the thrombocytopenic or the aplastic phase (Table 4).

Males exceed females, suggesting X-linked recessive inheritance in some cases. Recent data suggest that the defect in amega is impaired expression of the proto-oncogene c-Mpl, i.e., the receptor for TPO,[49] but whether the c-Mpl defect is primary or secondary remains to be identified.

Prenatal diagnosis of amega relies on demonstration of nonimmune thrombocytopenia in fetal blood, with normal radii confirmed by ultrasound (see the section on thrombocytopenia with absent radii).

Familial Aplastic Anemias

A large variety of families has been described with bone marrow failure; with dominant, recessive, or X-linked inheritance; with or without characteristic physical anomalies; and with normal results in clastogen-induced chromosome breakage tests. Detailed references are included in previous reviews.[8, 67] Penetrance seems variable, because some individuals may have anomalies without overt bone marrow problems and vice versa. There are also sporadic cases of persons who have birth defects who do not have FA, according to lymphocyte chromosome breakage analyses (which might need rethinking with regard to mosaicism, see above). In addition, a few patients who have known syndromes, such as Down's, Dubowitz's, Seckel's, Noonan's, Brachmann de Lange, and trisomies 13 and 18 have hypoproliferative cytopenias. In general, diagnoses are hematologically nonspecific and depend on the inheritance and the physical phenotype.

SINGLE CYTOPENIA

Diamond-Blackfan Anemia

Usually diagnosed within the first 6 months of life, Diamond-Blackfan (DBA) is inherited pure red-cell aplasia. Physical examination is often normal, although characteristic facies, short stature, and abnormal thumbs have been observed in as much as one third of patients (Table 1). Radiologic studies are consistent with the physical anomalies. Diagnostic criteria are normochromic, usually macrocytic anemia, reticulocytopenia, normocellular bone marrow with erythroid hypoplasia, normal or occasionally decreased white count, and normal or increased platelet count. Patients who have DBA are at risk for malignancies, including both leukemia and solid tumors (Table 4).

At presentation, blood counts may show macrocytic anemia, low reticulocyte counts, and increased HbF (Table 2). Although the majority of the bone marrows have erythroid aplasia, a few show normal or even increased erythroid precursors. Hematopoietic cultures have normal myeloid colony formation, with usually decreased erythroid colonies and bursts [colony-forming units-erythroid (CFU-E) and burst-forming units-erythroid (BFU-E)] (Table 3). Erythropoiesis in vitro may be improved with several manipulations, including decreased oxygen, high concentration of Ep, or addition of IL-3 or SCF.[6, 19] Serum levels of Ep are elevated more than predicted from the level of the anemia,[67] whereas levels of SCF are normal.[2] Increased apoptosis was demonstrated by withholding Ep from DBA cultures, resulting in accelerated loss of progenitors and DNA degradation.[51] A relatively specific test for DBA is increased red-cell adenosine deaminase (ADA); such increased ADA is found in ~90% of DBA patients.[29]

The inheritance of DBA includes ~75% sporadic, ~15% autosomal recessive, and ~10% autosomal dominant families (Table 5). Early karyotypes suggested abnormalities in either chromosome 1 or 16, but those results were not confirmed. Other candidate regions include the genes for kit and kit ligand, which are mutant in W and Sl mice with genetic macrocytic anemia, but Southern blots and even gene sequencing found no abnormalities of either of those genes.[1, 25] More recent studies mapped the DBA locus to a 1.8 Mb region of 19q13[32]; this region is an apparent candidate in all inheritance patterns.

Theoretically, prenatal diagnosis of DBA might be done in candidate families by use of fetal blood obtained by cordocentesis before 20 weeks gestation. The blood could be analyzed for hemoglobin (Hb), MCV, and perhaps red-cell ADA and erythroid progenitors. Fetal DNA from chorionic villi or amniocytes might be screened for linkage to 9q13 in the future. In practice, ultrasound has been used to look for cardiomegaly and effusions as early signs of hydrops from anemia,[47, 53] and altered cardiac blood flow velocities were seen in one possible case.[64] Intrauterine transfusions may be offered to facilitate continuation of the pregnancy.

The diagnosis of DBA should be considered in cases with nonimmune hydrops or macrocytic anemia in infancy and early childhood. It can be distinguished from transient erythroblastopenia of childhood (TEC) by the chronicity of DBA, the high MCV and HbF at presentation, and the reduction in erythroid progenitors in culture assays. B19 parvovirus may also cause neonatal hydrops and erythroid aplasia and may be indistinguishable from DBA.[14]

Kostmann's Syndrome

Severe congenital neutropenia, congenital agranulocytosis, or Kostmann's syndrome (KS), includes patients who have neutropenia identified early in infancy, often with a history of pyogenic infections. Only rarely are there associated birth defects (Table 1). The absolute neutrophil count is $<200/\mu L$ (Table 2), whereas eosinophils and monocytes may be increased. The bone marrow has normal cellularity, with a maturation arrest at the promyelocyte-myelocyte stage.[8, 67] Hematopoietic cultures may have normal or reduced numbers of myeloid colonies, and the cells in those colonies are eosinophils, monocytes, and early myeloid precursors. Differentiation to neutrophils occurs if G-CSF is added to the cultures (Table 3). MDS, monosomy 7, and acute myeloid leukemias have been reported in 5% to 10% of KS patients, many of whom had been treated with G-CSF (Table 4).[13] Serum levels of G-CSF are increased in KS patients.[48] Although a few patients were found to have acquired myeloid mutations of the cytoplasmic portion of the G-CSF receptor, this did not interfere with clinical response to G-CSF nor did it correlate with development of leukemia.[21] Monosomy 7 and activating proto-oncogene RAS mutations were noted to develop in G-CSF-treated patients who had KS and who had undergone malignant transformation to MDS or leukemia.[35]

KS is inherited as an autosomal recessive. G-CSF production is normal, and a candidate gene, the G-CSF receptor, was also found to be normal.[30] Prenatal diagnosis of KS would have to rely on demonstration of zero neutrophils in fetal blood, because the usual neutrophil count at 20 weeks gestation is $\leq 200/\mu L$.[26]

Thrombocytopenia with Absent Radii

An easy diagnosis is made in cases of thrombocytopenia with absent radii (TAR) because it is made in thrombocytopenic newborn infants who have bilateral radial absence, with thumbs present (Table 1). In contrast, thrombocytopenia in FA and trisomy 18, and radial aplasia are associated with absent or abnormal thumbs. Radiologic studies are useful to document the extent and details of the skeletal abnormalities. Blood counts reveal decreased numbers of platelets, usually $<50,000/\mu L$, anemia secondary to bleeding and with reticulocyte response, and leukocytosis in many infants.[8] HbF and MCV are normal for age and are consistent with a single cytopenia. Platelet function is usually normal, when a sufficient number of platelets is available for reliable testing.[11] Karyotypes and chromosome breakage analyses are also normal. Bone marrow examination shows normal cellularity, normal myeloid and erythroid precursors, and absent or decreased megakaryocytes, which are hypoplastic, small, and immature. In many patients, the thrombocytopenia improves with age. Only one case of acute lymphocytic leukemia was reported and that may be coincidental.[16]

Most reports indicate decreased or absent megakaryocyte colony formation in hematopoietic culture assays, as well as failure to improve with the addition of TPO. Serum TPO was increased, and the TPO receptor, c-Mpl, was expressed normally on the platelets in TAR, but there was a lack of response to TPO in the signal transduction pathway.[11]

Most cases of TAR appear to be autosomal recessive, although there are a few apparently dominant families. Prenatal diagnosis can be done by a combination of ultrasound demonstration of radial aplasia and cordocentesis for fetal thrombocytopenia.[22]

SUMMARY

Laboratory diagnosis of inherited bone marrow failure syndromes includes general evaluations, such as blood counts, examination of the peripheral blood smear for morphology, and bone marrow aspirates and biopsies, which may help the clinician classify the patient, particularly if there are no characteristic physical anomalies. Specific diagnoses require unique tests that are only available for a few of the diagnoses. The most useful is chromosome breakage in the diagnosis of FA, with gene mutation analysis or mapping about to become the gold standard when all of the FA genes have been cloned. The diagnosis of DC remains clinical at this time, although linkage to Xq28 and skewed maternal X inactivation may be helpful in some families. Laboratory proof of SD may be provided by decreased serum trypsinogen or other evidence of exocrine pancreatic insufficiency. CHH is substantiated when absent central pigment in hair is found and when it is mapped to 9p21-p13. The only mitochondrial syndrome, PS, is proved with demonstration of deleted mitochondrial DNA. RD is diagnosed from blood and marrow studies that demonstrate lack of lymphoid as well as myeloid activity. Amega requires absent or abnormal marrow megakaryocytes; if radii are also absent, the diagnosis is TAR. DBA usually has elevated red-cell ADA, and the DBA locus may map to 19q13. KS is diagnosed in patients who have congenital nonimmune severe neutropenia. Clinical suspicion of particular diagnoses can often be substantiated by laboratory tests of varying specificity.

References

1. Abkowitz JL, Broudy VC, Bennett LG, et al: Absence of abnormalities of c-kit or its ligand in two patients with Diamond-Blackfan anemia. Blood 79:25, 1992
2. Abkowitz JL, Hume H, Yancik SA, et al: Stem cell factor serum levels may not be clinically relevant. Blood 87:4017, 1996
3. Alter BP: Fetal erythropoiesis in stress hematopoiesis. Exp Hematol 7:200, 1979
4. Alter BP: Arm anomalies and bone marrow failure may go hand in hand. Am J Hand Surg 17:566, 1991
5. Alter BP: Fanconi's anemia and malignancies. Am J Hematol 53:99, 1996
6. Alter BP, Knobloch ME, He L, et al: Effect of stem cell factor on in vitro erythropoiesis in patients with bone marrow failure syndromes. Blood 80:3000, 1992
7. Alter BP, Knobloch ME, Weinberg RS: Erythropoiesis in Fanconi's anemia. Blood 78:602, 1991
8. Alter BP, Young NS: The bone marrow failure syndromes. *In* Nathan DG, Orkin SH (eds): Hematology of Infancy and Childhood. Philadelphia, PA, WB Saunders, 1998, p 237
9. Arkin S, Brodtman D, Alter BP, et al: A screening test for Fanconi anemia using flow cytometry [abstract]. Blood 82:176A, 1993
10. Auerbach AD, Alter BP: Prenatal and postnatal diagnosis of aplastic anemia. *In* Alter BP (ed): Methods in Hematology: Perinatal Hematology. Edinburgh, Churchill Livingstone, 1989, p 225
11. Ballmaier M, Schulze H, Strauss G, et al: Thrombopoietin in patients with congenital thrombocytopenia and absent radii: Elevated serum levels, normal receptor expression, but defective reactivity to thrombopoietin. Blood 90:612, 1997
12. Berger R, Coniat ML, Gendron MC: Fanconi anemia. Chromosome breakage and cell cycle studies. Cancer Genet Cytogenet 69:13, 1993
13. Boxer LA, Dale D: Congenital neutropenia and the risk of leukemia. J Pediatr 130:335, 1997
14. Brown KE, Green SW, Antunez de Mayolo J, et al: Congenital anaemia after transplacental B19 parvovirus infection. Lancet 343:895, 1994
15. Butturini A, Gale RP, Verlander PC, et al: Hematologic abnormalities in Fanconi anemia: An International Fanconi Anemia Registry study. Blood 84:1650, 1994
16. Camitta BM, Rock A: Acute lymphoidic leukemia in a patient with thrombocytopenia/absent radii (TAR) syndrome. Am J Pediatr Hematol Oncol 15:335, 1993
17. Cervenka J, Arthur D, Yasis C: Mitomycin C test for diagnostic differentiation of idiopathic aplastic anemia and Fanconi anemia. Pediatrics 67:119, 1981
18. Devriendt K, Matthijs G, Legius E, et al: Skewed X-chromosome inactivation in female carriers of dyskeratosis congenita. Am J Hum Genet 60:581, 1997
19. Dianzani I, Garelli E, Crescenzio N, et al: Diamond-Blackfan anemia: Expansion of erythroid progenitors in vitro by IL-9, but exclusion of a significant pathogenetic role

for the IL-9 gene and the hematopoietic gene cluster on chromosome 5q. Exp Hematol 25:1270, 1997
20. Dokal I, Luzzatto L: Dyskeratosis congenita is a chromosomal instability disorder. Leuk Lymphoma 15:1, 1994
21. Donadieu J: Pathophysiology of Kostmann syndrome: The G-CSF receptor issue. Hematol Cell Ther 39:102, 1997
22. Donnenfeld AE, Wiseman B, Lavi E, et al: Prenatal diagnosis of thrombocytopenia absent radius syndrome by ultrasound and cordocentesis. Prenat Diagn 10:29, 1990
23. Drachtman RA, Alter BP: Dyskeratosis congenita: Clinical and genetic heterogeneity. Report of a new case and review of the literature. Am J Pediatr Hematol Oncol 14:297, 1992
24. Drachtman RA, Alter BP: Dyskeratosis congenita. Dermatol Clin 13:33, 1995
25. Drachtman RA, Geissler EN, Alter BP: The SCF and c-kit genes in Diamond-Blackfan anemia. Blood 79:2177, 1992
26. Forestier F, Daffos F, Galacteros F, et al: Hematological values of 163 normal fetuses between 18 and 30 weeks of gestation. Pediatr Res 20:342, 1986
27. Giampietro PF, Verlander PC, Davis JG, et al: Diagnosis of Fanconi anemia in patients without congenital malformations: An International Fanconi Anemia Registry study. Am J Med Genet 68:58, 1997
28. Gillio AP, Verlander PC, Batish SD, et al: Phenotypic consequences of mutations in the Fanconi anemia FAC gene: An International Fanconi Anemia Registry study. Blood 90:105, 1997
29. Glader BE, Backer K: Elevated red cell adenosine deaminase activity: A marker of disordered erythropoiesis in Diamond-Blackfan anaemia and other haematologic diseases. Br J Haematol 68:165, 1988
30. Guba SC, Sartor CA, Hutchinson R, et al: Granulocyte colony-stimulating factor (G-CSF) production and G-CSF receptor structure in patients with congenital neutropenia. Blood 83:1486, 1994
31. Guinan EC, Lee YS, Lopez KD, et al: Effects of interleukin-3 and granulocyte-macrophage colony-stimulating factor on thrombopoiesis in congenital amegakaryocytic thrombocytopenia. Blood 81:1691, 1993
32. Gustavsson P, Willing T-N, van Haeringen A, et al: Diamond-Blackfan anaemia: Genetic homogeneity for a gene on chromosome 19q13 restricted to 1.8 Mb. Nat Genet 16:368, 1997
33. Jakobs PM, Fiddler-Odell E, Reifsteck C, et al: Complementation group assignments in Fanconi anemia fibroblast cell lines from North America. Somat Cell Mol Genet 23:1, 1997
34. Joenje H, Oostra AB, Wijker M, et al: Evidence for at least eight Fanconi anemia genes. Am J Hum Genet 61:940, 1997
35. Kalra R, Dale D, Freedman M, et al: Monosomy 7 and activating RAS mutations accompany malignant transformation in patients with congenital neutropenia. Blood 86:4579, 1995
36. Knight SW, Vulliamy T, Forni GL, et al: Fine mapping of the dyskeratosis congenita locus in Xq28. J Med Genet 33:993, 1996
37. Kupfer GM, Naf D, Suliman A, et al: The Fanconi anaemia proteins, FAA and FAC, interact to form a nuclear complex. Nat Genet 17:487, 1997
38. Kwee ML, van der Kleij JM, van Essen AJ, et al: An atypical case of Fanconi anemia in elderly sibs. Am J Med Genet 68:362, 1997
39. Lacaille F, Mani TM, Brunelle F, et al: Magnetic resonance imaging for diagnosis of Shwachman's syndrome. J Pediatr Gastroenterol Nutr 23:599, 1996
40. Lo Ten Foe JR, Kwee ML, Rooimans MA, et al: Somatic mosaicism in Fanconi anemia: Molecular basis and clinical significance. Eur J Hum Genet 5:137, 1997
41. Lo Ten Foe JR, Rooimans MA, Bosnoyan-Collins L, et al: Expression cloning of a cDNA for the major Fanconi anaemia gene, FAA. Nat Genet 14:320, 1996
42. Lucky AW: Pigmentary abnormalities in genetic disorders. Dermatol Clin 6:193, 1988
43. Lyman SD, Seaberg M, Hanna R, et al: Plasma/serum levels of flt3 ligand are low in normal individuals and highly elevated in patients with Fanconi anemia and acquired aplastic anemia. Blood 86:4091, 1995

44. Mack DR, Forstner GG, Wilschanski M, et al: Shwachman syndrome: Exocrine pancreatic dysfunction and variable phenotypic expression. Gastroenterology 111:1593, 1996
45. Makitie O, Kaitila I: Cartilage-hair hypoplasia - Clinical manifestations in 108 Finnish patients. Eur J Pediatr 152:211, 1993
46. McKusick VA, Eldridge R, Hostetler JA, et al: Dwarfism in the Amish. II. Cartilage-hair hypoplasia. Bull Johns Hopkins Hosp 116:285, 1965
47. McLennan AC, Chitty LS, Rissik J, et al: Prenatal diagnosis of Blackfan-Diamond syndrome: Case report and review of the literature. Prenat Diagn 16:349, 1996
48. Mempel K, Pietsch T, Menzel T, et al: Increased serum levels of granulocyte colony-stimulating factor in patients with severe congenital neutropenia. Blood 77:1919, 1991
49. Muraoka K, Ishii E, Tsuji K, et al: Defective response to thrombopoietin and impaired expression of c-mpl mRNA of bone marrow cells in congenital amegakaryocytic thrombocytopenia. Br J Haematol 96:287, 1997
50. Pearson HA, Lobel JS, Kocoshis SA, et al: A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. J Pediatr 95:976, 1979
51. Perdahl EB, Naprstek BL, Wallace WC, et al: Erythroid failure in Diamond-Blackfan anemia is characterized by apoptosis. Blood 83:645, 1994
52. Polmar SH, Pierce GF: Cartilage hair hypoplasia: Immunological aspects and their clinical implications. Clin Immunol Immunopathol 40:87, 1986
53. Rogers BB, Bloom SL, Buchanan GR: Autosomal dominantly inherited Diamond Blackfan anemia resulting in nonimmune hydrops. Obstet Gynecol 89:805, 1997
54. Rose C, Bauters F, Galacteros F: Hydroxyurea therapy in highly unstable hemoglobin carriers. Blood 88:2807, 1996
55. Rotig A, Cormier V, Blanche S, et al: Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. J Clin Invest 86:1601, 1990
56. Schultz JC, Shahidi NT: Tumor necrosis factor-a overproduction in Fanconi's anemia. Am J Hematol 42:196, 1993
57. Smith O, Hann IM, Chessells JM, et al: Haematological abnormalities in Shwachman-Diamond syndrome. Br J Haematol 94:279, 1996
58. Strathdee CA, Duncan AMV, Buchwald M: Evidence for at least four Fanconi anaemia genes including FACC on chromosome 9. Nat Genet 1:196, 1992
59. Strathdee CA, Gavish H, Shannon WR, et al: Cloning of cDNAs for Fanconi's anaemia by functional complementation. Nature 356:763, 1992
60. Sulisalo T, Klockars J, Makitie O, et al: High-resolution linkage-disequilibrium mapping of the cartilage-hair hypoplasia gene. Am J Hum Genet 55:937, 1994
61. Sulisalo T, Sillence D, Wilson M, et al: Early prenatal diagnosis of cartilage-hair hypooplasia (CHH) with polymorphic DNA markers. Prenat Diagn 15:135, 1995
62. The Fanconi Anaemia/Breast Cancer Consortium: Positional cloning of the Fanconi anaemia group A gene. Nat Genet 14:324, 1996
63. Verlander PC, Kaporis A, Liu Q, et al: Carrier frequency of the IVS4 + 4 A $\rightarrow$ T mutation of the Fanconi anemia gene FAC in the Ashkenazi Jewish population. Blood 86:4034, 1995
64. Visser GHA, Desmedt MCH, Meijboom EJ: Altered fetal cardiac flow patterns in pure red cell anaemia (the Blackfan-Diamond syndrome). Prenat Diagn 8:525, 1988
65. Whitney M, Thayer M, Reifsteck C, et al: Microcell mediated chromosome transfer maps the Fanconi anaemia group D gene to chromosome 3p. Nat Genet 11:341, 1995
66. Wunder E, Mortensen BT, Schilling F, et al: Anomalous plasma concentrations and impaired secretion of growth factors in Fanconi's anemia. Stem Cells 11:144, 1993
67. Young NS, Alter BP: Aplastic Anemia: Acquired and Inherited. Philadelphia, PA, WB Saunders, 1994, p 410

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